SACRAMENTO MEDICAL FOUNDATION | Blood Centers

September 27, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Number 97D-03 18

Dear Sir:

SACRAMENTO BLOOD CENTER
1625 Stockton Boulevard
Sacramento, CA 95816-7089
TEL 916456-1500
FAX 916452-9232

NORTH STATE BLOOD CENTER
1880 Park Marina Drive
Redding, CA 96001
TEL 530243-0160
FAX 530243-0580

NORTH VALLEY BLOOD CENTER
285 Cohasset Road
Chico, CA 95926
TEL 530893-5433
FAX 530893-2537

CENTER FOR BLOOD RESEARCH
1631 Stockton Boulevard
Sacramento, CA 95816-7089
TEL 916456-1500
FAX 916456-2414

As published in the August 17, 1999 Federal Register, I wish to provide comments on the above-referenced Docket number concerning the Guidance for Industry entitled, **"Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products."** I appreciate the opportunity to provide input within the sixty-day comment period and trust that my comments will be of assistance to the agency in formulating its precautionary measures to reduce the possible risk of transmission of CJD and nvCJD via blood and plasma products.

I note in the Introduction, under item No. 2, that this guidance has been released for potential immediate implementation, even during the comment period, because **"there are public health reasons for immediate implementation of the recommendations regarding additional safeguards with respect to new variant CJD."** In the revised document, these important "public health reasons" should be spelled out, because they are not evident in the document, nor from the available literature.

In **Item II. B, on page 4**, the **"rationale for withdrawing plasma derivatives from donors with nvCJD"** is provided. On the next page, the features which would lead one to diagnose "suspected" nvCJD are listed; but it is not clear whether blood and blood components, or plasma derivatives, from patients with "suspected nvCJD" should be withdrawn, or only those with documented nvCJD.

In **Section III.** A.2, it is stated that donors with increased risk of CJD be **"appropriately counseled,"** presumably as part of the deferral process. Is this true, even if only one of their blood relatives has CJD? What appropriate counseling is suggested for these individuals, who are at extremely low risk of developing CJD and can do nothing tc prevent its occurrence? Further, why not restrict those at risk to individuals who have two or more blood relatives with CJD? This was the prior policy!

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In **Section** TlT.A.3, donors who have resided in the United Kingdom (UK) from 1980 to 1996 for six months or more, cumulatively, are to be indefinitely deferred. The rationale for selecting six months versus one year, or one month, or any other time period, should be specified. What degree or percent risk reduction is anticipated by the six month period? Based on what evidence? Further, the criteria for rescinding this recommendation should be spelled out, as well as any data or evidence which would cause the deferral to be extended to other countries with imported or endemic bovine spongiform encephalopathy (BSE) should be detailed, too. Actually, the unsupported deferral for 6 months of UK residence should be deleted, or replaced with one based on some data, e.g., the 41 UK cases of nvCJD were born in the UK and lived there for 10 years between 1980 and 1996.

Section HI.A.4. Since donors who received injections of products made from cattle in "BSE endemic countries" are also to be indefinitely deferred, the FDA should spell out what these injectable products are, and what countries are considered "endemic" for BSE. Further, for those countries which have imported as opposed to endemic BSE, why does this not apply to those countries, too?

In **Section III.C**, recommendations are provided regarding donor reentry after donor deferral of risk for familial CJD. For Section D, there should be similar recommendations regarding donor reentry after deferral for residence in the United Kingdom for six months or more. In other words, what criteria, data, experiments, etc. would enable the rescinding of this indefinite deferral of temporary residents of the United Kingdom? Further, the FDA may wish to spell out what criteria would similarly invoke deferral for temporary residence in countries like France and Ireland, where at least one case of nvCJD has occurred.

For **Section III.D.2**, the FDA should spell out those countries which are considered "BSE affected" versus those which are "BSE endemic." In addition, in this section, in the suggested question, the definition of "knowingly" should be provided.

In **Section IV. A.1**, those in-date blood components, which come from donors at potential risk of transmitting CJD, or nvCJD, are to be identified and withdrawn. If it is okay to use and transfuse components from these donors until the guidance document is adopted, e.g., on February 17, 2000, why is it recommended that they be recalled, if not used by then? In **Section 2** of this, what notification should be provided to consignees, and should this be passed on to potential recipients, and for what purpose?

In **Section IV.B,** regarding recall of plasma derivatives, it is stated that when materials come from donors with CJD, CJD risk factors, or potential exposure to nvCJD, their pooled plasma intermediates and derivatives should not be

withdrawn. However, in the next section, plasma from these individuals, which has not yet been pooled, should be withdrawn. These two recommendations appear to be inconsistent. They should either both be withdrawn, or neither be withdrawn.

In **Section V**, re additional recommendations regarding consignee notification and counseling, what is the definition of "readily retrievable records"? If it takes five (5) working days to find something, it is not readily retrievable. If records can be found in one (1) hour, or less, then such records are readily retrievable. What counseling is recommended regarding the theoretical risk at which these patients may be'?

In **Section VI**, regarding requirements, it is acknowledged that there has been **"no transmission of CJD or nvCJD by human blood components or plasma derivatives...".** Nevertheless, the FDA is recommending that all components include a warning label to address the theoretical risk of CJD and nvCJD. The warnings provided may vary depending on whether the material is albumin or a blood component, or a plasma derivative; however, it would seem that the wording should be the same, based upon the initial statement that there has been no documentation of transmission by any of these. Further, if this theoretical risk, i.e., of CJD and nvCJD, is to be mentioned, why not other theoretical risks? What about other real risks which have been documented and are not theoretical, but actual? Why not mention bacterial transmission, a real risk? The FDA should detail why the theoretical risk of CJD should be noted, while other theoretical and actual risks, not currently mentioned, are not to be so noted.

In **Section VII, Implementation of Recommendations**, it is suggested that "alternative" approaches to the recommendations, which provide "equivalent" protection, may be submitted for discussion with the FDA. There is no evidence that the proposed guidelines herein will provide any protection; there is a disclaimer that they are simply precautionary to reduce a theoretical risk. Thus, it would be difficult to provide alternative recommendations which would purport to give equivalent protection, i.e., the same reduction of a theoretical risk. In any case, it should be noted that leukoreduction is an alternative and there is, in fact, some experimental evidence to support this approach, certainly more than the evidence (or contrary evidence) to support these new FDA recommendations, especially regarding deferral of individuals who resided for six months or more in the UK between 1980 and 1996. The FDA should specify what the protection envisaged by these new recommendations would provide, so those alternatives with comparable (envisaged) efficacy can be proposed. For example, could prospective donors who have ingested more than x liters of French wine in the last twenty years be deferred as donors for comparable efficacy in reducing the theoretical risk of nvCJD transmission?

The above recommendations, if implemented, will have a devastating impact on the American blood supply, which is already insufficient. Projections for the coming year indicate that expected usage will exceed the anticipated supply, even without implementation of these guidelines! In support of this, I enclose relevant sections of the **Report on Blood Collection and Transfusion in the United States** in 1997, prepared by the National Blood Data Resources Center. I refer you specifically to Figure 6, on which I have added the projections for the year 2000 when usage will exceed collections by approximately 200,000 units, I also direct your attention to Figure 5, which shows that, as the percent of donations from first-time donors increases, the percent due to reactive test loss also increases. While this is a measure of reactive tests, it is also a measure (indirectly) of falsely negative tests. Thus, by dramatically increasing the number of first-time donors to make up for those (mostly repeat donors) lost by the recommendations in this guidance document, we will more likely increase real risk to patients of known transfusion-transmitted agents, while attempting to decrease the theoretical risk of CJD and nvCJD. Therefore, it is especially important that, in the revised guidance document, the FDA carefully spell out what criteria, data, information, etc. would be acceptable to rescind these recommendations, especially the new UK deferral policy as stated. Then, the specific criteria outlined, which are responsive, may be used to gather appropriate data. Without such criteria, and the required data, spelled out, the guidelines will likely not be rescinded in the foreseeable future.

Thank you for the opportunity to comment on this "guidance for industry." I look forward to seeing a revised version, responsive to the above concerns, as well as those raised by other individuals and organizations.

Sincerely,

Paul Holland

Paul V. Holland, M.D.
Medical Director/Chief Executive Officer

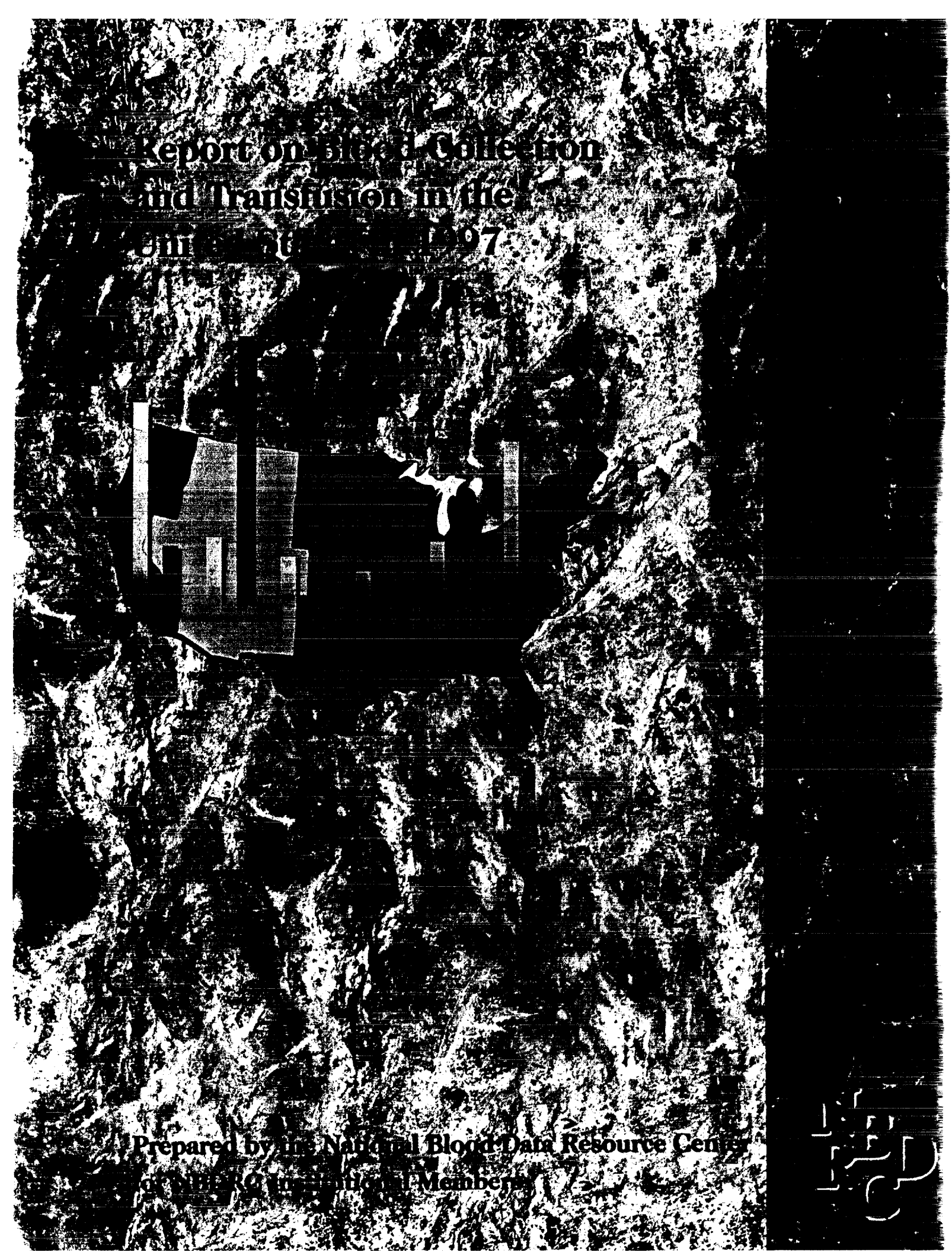
PVH:rc 323.99

Enclosure

PC: Louis Katz, MD
America's Blood Centers
725 15th Street, NW
Suite 700
Washington, DC 20005

Susan Wilkinson, EdD
President
American Association of Blood Banks
8101 Glenbrook Road
Bethesda, MD 20814 2749

Report on Blood Collection and Transfusion in the United States, 1997



Prepared by the National Blood Data Resource Center

of the AABB Institutional Members

Nationwide Blood Collection and Utilization Survey

Survey Objectives

This report presents the results of the first *Nationwide Blood Collection and Utilization* Survey conducted by the National Blood Data Resource Center (NBDRC) in 1998. This survey of blood services activities in the United States (U.S.) was intended to replace both the Annual Institutional Questionnaire of the American Association of Blood Banks (AABB), and the series of national surveys previously conducted by the Center for Blood Research. It was designed to capture quantitative data regarding **blood** collection, processing and transfusion, as well as other information relevant to blood banking and transfusion medicine.

Survey Methods

The sampling frame for this survey consisted of two parts, the AABB institutional member list and the American Hospital Association (AHA) list of hospitals. All AABB members, including 150 blood centers and 1,892 hospitals, were selected. One U.S. blood center that is not a member of AABB was also included for completeness.

Eligible non-AABB-member hospitals from the AHA list were stratified based on number of inpatient surgeries performed or on number of hospital beds if data on surgeries were unavailable. Number of surgeries was considered to be the variable most strongly associated with blood collections. The sample of 1,410 non-AABB hospitals was then selected using stratified systematic random sampling.

Initially, sampled institutions were sent the full 14-page survey questionnaire in February 1998. Reminder post-cards were mailed to all non-respondents after eight weeks. Non-responding blood centers were contacted by telephone. Because response rates were low in some strata, a shortened instrument was sent to non-respondents in September 1998.

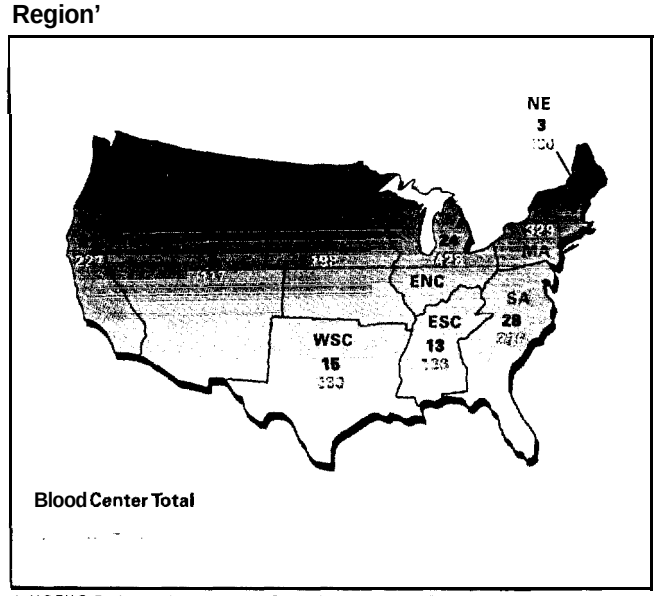
Non-U.S. blood centers and hospitals, as well as military hospitals, were removed from the database prior to analysis to ensure comparability with previous surveys of U.S. domestic institutions.

Survey Respondents

Response rates were: blood centers 99% (147/149); AABB-member hospitals, 8 1% (1,498/1 ,841); and non-AABB-member hospitals, 51% (715/1,410). **Figure** 1 illustrates the distribution of responding blood centers and hospitals among nine geographic regions as defined by the United States Public Health Service (U.S.P.H.S.).

As the response rate of U.S. blood centers was nearly 100%, no further adjustment was necessary. However, the hospital **data** were adjusted for non-response. Weighting of the data within each hospital group allowed for the calculation of national estimates for some of the key collection and transfusion variables. Hospital non-response is reflected in the confidence intervals (CI) reported for these estimates. A full description of the statistical methods employed in the analysis of the data and the limitations of the survey can be obtained from the National Blood Data Resource Center.

Figure 1. Distribution of Blood Center (n = 147) and Hospital (n = 2204) Respondents by U.S.P.H.S. Region'



' U.S.P.H.S. Regions and Abbreviations: Pacific (PAC); Mountain (MT); West North Central (WNC); West South Central (WSC); East North Central (ENC); East South Central (ESC); New England (NE); Mid-Atlantic (MA); South Atlantic (SA)

Table 1. Estimates of 1997 Blood Services Activities of U.S. Blood Centers and Hospitals for Whole Blood (WB) and Red Cells (RBC) (expressed in thousands of units)

Activity	Blood Centers	Hospitals		Combined Total	% of Total Collections/ Transfusions	Percentage Change 1994–1997
		Total	95%CI			
Collections						
Allogeneic (excluding directed)'	11,031	710	214	11,741	93.3	-0.27
Autologous	386	257	33	643	5.1	-36.5
Directed	132	72	20	205	1.6	-38.6
Total Supply	11,550	1,050	222	12,602	100.0	-5.5
Rejected on testing	205	26	6	232	1.9	-45.7
Available supply	11,345	1,024		12,370	98.1	-4.0
Transfusions						
Allogeneic (excluding directed)	275 13	10,654	543	10,929	94.8	+7.1
Autologous		407	37	420	3.7	-12.9
Directed	3	78	11	81	0.7	-22.9
Pediatric'	2	87	18	89	0.8	-7.3
Total transfusions	292	11,224	588	11,517	100.0	+3.7
Untransfused WB/RBCs						
Outdated'	264	402		666	5.3	-11.7
Unaccounted for'				133	1.0	

* Non-U.S. imports (<200,000) included in allogeneic collection total
† Expressed as adult equivalent units
¥ Based on reported outdates only
ª Calculated value

Table 2. Estimates of 1997 Blood Services Activities of U.S. Blood Centers and Hospitals for Non-Red Cell Components (expressed in thousands of units)

Activity	Blood Centers	Hospitals		Combined Total	1994 Total	Percentage Change 1994–1997
		Total	95%CI			
Collections						
Single Donor Platelets'	830	151	45	981	820	+19.7
Platelet Concentrates	4,636	355	99	4,991	5,741	-13.1
FFP/Single Donor Plasma'	2,940	370	90	3,310	3,532	- 6.3
Cryoprecipitate	1,146	54	27	1,199	1,001	+19.8
Transfusions						
Single Donor Platelets	153	5,487	625	5,640 (940*)	4,284 (714*)	+31.7
Platelet Concentrates	132	3,265	413	3,396	3,582	-5.2
Total Platelets	285	8,752		9,037	7,866	+14.9
FFP/Single Donor Plasma	107	3,212	252	3,320	2,621	+26.7
Cryoprecipitate	31	785	101	816	713	+14.4
Outdated Non-RBC Components*	922	568	54	1,490	1,316	+13.2

* Expressed in thousands of packs
† For transfusions; includes apheresis plasma
¥ Based on reported outdates only

Current Issues in Blood Collection and Screening

Screening Test Losses

The overall loss of donated whole blood units due to infectious disease screening tests was 1.9%. The percentage of blood center collections discarded for this reason was 1.8% (147 blood centers reporting). **Table 6** shows the proportion of donation test losses for each geographic region as a function of proportional allogeneic whole blood collections at reporting centers (ARC not included).

Test losses differed significantly between reporting blood centers in different U.S.P.H.S. regions (range 154.4/10,000–77.3/10,000). The highest losses were experienced by collectors in southern areas of the U.S., while the lowest were experienced by the New England/Mid-Atlantic and western areas. Numerous factors influence test loss, including demographics of the available donor pool, proportion of first time donors, and average frequency of annual donations by repeat donors.

Among hospitals, test loss was 3.3% of donations, reflecting the relatively higher proportion of first time donors at many hospital collection sites (see below).

The overall loss of allogeneic whole blood units due to infectious disease screening tests was 1.9% of allogeneic collections, or 232,000 units. This was 200,000 fewer units than were discarded three years previously. The significant decline ($p = .0006$) in the percentage of allogeneic units rejected, from 3.6% to 1.9%. is likely due to a combination of factors, including the elimination of the alanine amino-transferase (ALT) testing requirement, the increase in ALT cut-off (for sites that still conduct ALT measurements), and the fact that no new screening tests were introduced during 1997.

The proportion of units lost per screening test is displayed in **Table** 7. As expected, 1997 test loss rates (number of units discarded due to a particular test per 10,000 donations) did not differ from 1994 rates, with the exception of ALT testing. ALT-related test loss decreased from 180 to 30 units lost per 10,000, reflecting the changes noted above.

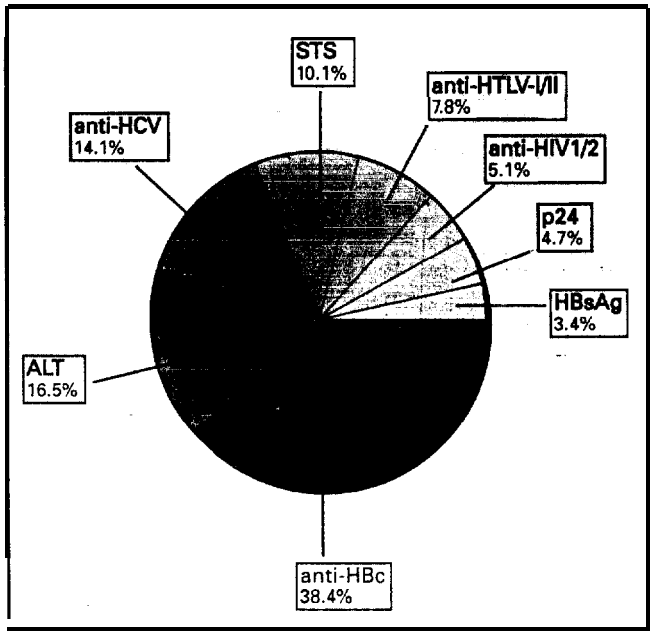
A total of 38.4% of the reported test loss was due to the continued implementation of anti-HBc testing (for which no confirmatory procedures are available) (see **Figure 3).** While measurement of ALT levels in donated blood is no longer required as a standard in the U.S., most blood centers continue to test and to discard blood with high ALT elevations (> 120 IU/L) to meet European requirements for acceptable recovered plasma. Serologic tests for viral markers and the serologic test for Syphilis (STS) accounted for the balance of the test loss.

Confirmatory Tests

While screening test losses described above are important in the context of collected units lost to the community blood supply, nearly 20,000 donations in 1997 were confumed positive for infectious disease markers. With ALT-elevated, anti-HBc-reactive, and p24 Ag-reactive units removed from the denominator, the overall percentage of screening test positive units was 24.4, reflecting the relatively poor specificity of such tests when applied to a low prevalence population. In most cases, these results indicate current infections that were detected prior to being transmitted to a recipient (the exception being STS which arguably reflects past infection only).

As shown in **Tables 8** and 9, the prevalence of confirmed infectious disease markers in blood collected by hospitals did not differ greatly from the rates observed among blood center donations.

Figure 3. Proportion of Total Screening Test Losses Due to Individual Tests for Reporting Blood Centers (n = 100)



Confidential Unit Exclusion (CUE)

Confidential unit exclusion (CUE) is a procedure by which donors may indicate confidentially whether their blood is suitable for transfusion. The effectiveness of the CUE practice in improving blood safety is controversial and the FDA made the use of CUB optional in 1993. Prior to this survey, it was unknown what proportion of blood centers and hospitals chose to continue the practice.

A total of 70.5% of 139 reporting blood centers and 40.5% of reporting hospitals currently use confidential unit exclusion as part of their standard operating procedures. As shown in **Figure** 4, there is a clear geographical correlation with CUE policy that favors its use by blood centers in the northern and eastern portions of the country.

Table 10 shows the overall U.S. and regional rates of donations lost to CUE among blood centers that use the CUE procedure. One criticism of the CUB procedure is that a high proportion of donors who choose to exclude their donation do so because they misunderstand the procedure, rather than because they have an unrevealed risk factor.

First Time Donors

The definition of a first time blood donor, while seemingly straightforward, is actually somewhat complex. A first time blood donor is generally defined by a blood collection entity as an individual who is donating at that facility for the first time. Because first time donors are less likely to return for subsequent donation, are more likely to be deferred for medical/behavioral history, and are more likely to be reactive on a laboratory screening test, they represent a greater proportional effort per unit of whole blood collected than do repeat donors.'

The median percentage of donations made by first time donors reported by blood centers in this survey was 20%. The median percentage of donations made by first time donors at hospital-based collection sites was 21%. The combined median for all U.S. collections in 1997 was 20%. While 56.2% of all blood centers collect blood from a donation base having < 20% first time-donors, donations from first time donors exceeding 40% are &awn by 7.3% of the nation's blood centers.

The proportion of donations from first time donors at U.S. hospitals is bi-modal with approximately one-third of hospitals having few first time donors, and slightly less than one-third using first time donors for more than one-half of their collections.

The percentage of donations from first time donors varies considerably throughout different geographic areas of the U.S., with lowest proportions observed in the upper Midwest and the highest proportions in the eastern and southern areas of the country, **Figure 5** illustrates the direct relationship between test loss and the proportion of donations from first time donors.

Figure 4. Proportion of Reporting Blood Centers that use Confidential Unit Exclusion (CUE) by U.S.P.H.S Region (n = 139')

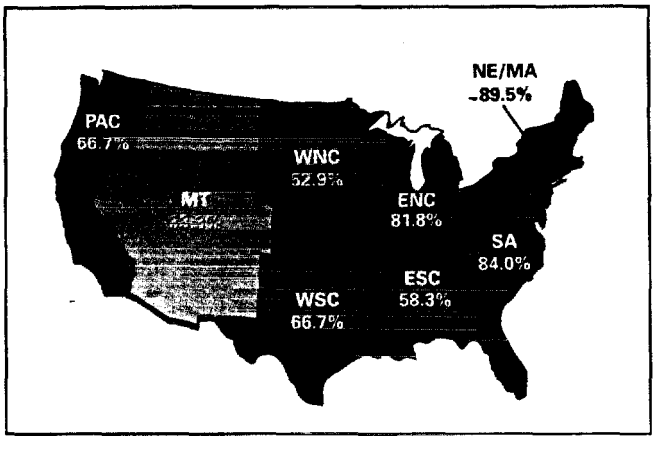
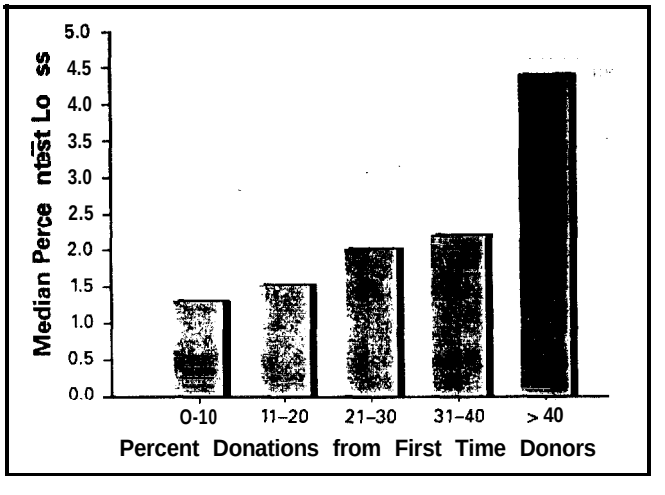


Figure 5. Blood Center Screening Test Loss by Percent Donations from First Time Donors (n = 941



Conclusions

Key Findings

The *1998 Nationwide Blood Collection and Utilization* Survey data, for the most part, extend the trends documented by the final surveys conducted by the Center for Blood Research in 1992 and 1994. However, some significant results are noteworthy.

Autologous and directed donations decreased substantially, while allogeneic collections were essentially stable. The number of allogeneic units (community and directed donations) rejected as a result of laboratory screening tests was significantly lower. This further lessened the impact of the overall decline in donations on the available supply.

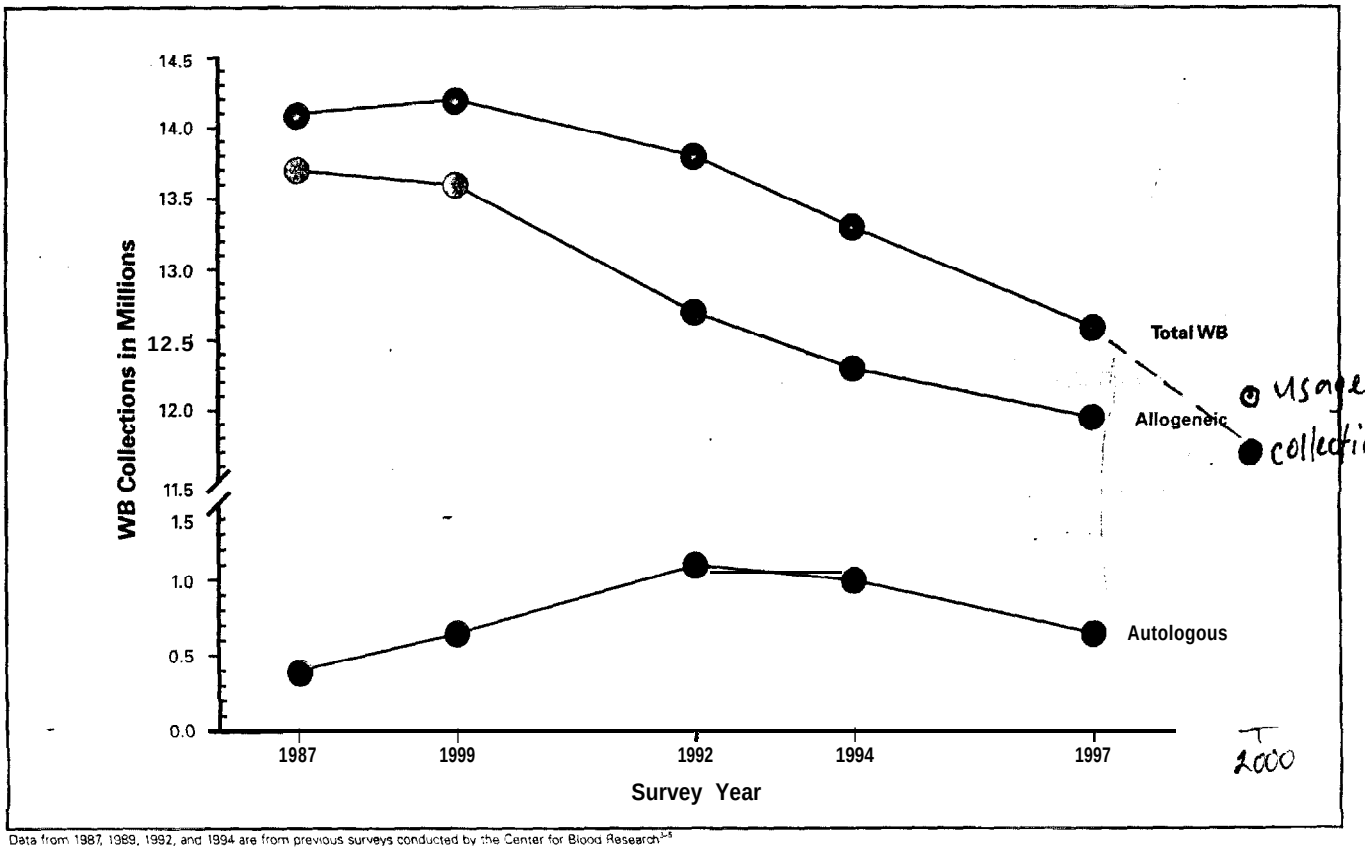
Similarly, the transfusion of autologous and directed units declined in 1997. However, significantly fewer autologous units were discarded unused, and moredirected units were crossed over-by hospitals to the community supply.

The proportion of units leukofiltered before or after storage increased measurably, perhaps influenced by recent policy discussions regarding universal leukoreduction.

Although the utilization of red cells remained stable, the transfusion of most non-RBC components showed significant growth. The transfusion of platelets rose sharply, driven by a significant increase in the collection and utilization of single donor apheresis platelets. The use of cryoprecipitate and FFP/single donor plasma for transfusion also increased.

With the exception of platelet concentrates, a lower proportion of all RBC and non-RBC components was discarded or otherwise unaccounted for.

Figure 6. Allogeneic, Autologous, and Total Whole Blood (WB) Collections (1987-1997)



Data from 1987, 1989, 1992, and 1994 are from previous surveys conducted by the Center for Blood Research[3-5]

FIRST CLASS MAIL

Sacramento Medical Foundation
Blood Center
1625 *Stockton Blvd.*
Sacramento, ***CA 95816-7089***
24 hour - (976) ***731-7100***

TO:

DOCKETS MANAGEMENT BRANCH
HFA-305
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE ROOM 1061
ROCKVILLE MD 20852